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Marital and Reproductive Histories of Women With Cancer of the Breast and Their Sisters

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In a study of 45 pairs of sisters—each pair including one sister with cancer of the breast and one without the disease—differences in marital and reproductive histories were observed. These differences included less frequent marriage, later marriage, fewer children, and a longer delay between date of marriage and the first pregnancy in the sisters with the disease. These findings appear to confirm presently known reproductive risk factors for cancer of the breast, but they also raise the possibility that unknown behavioral factors influencing the endocrine system may be delaying marriage and pregnancy.

A NUMBER OF ARTICLES[1-5] have reported an association between the risk of cancer of the breast and women's reproductive histories. This association is based primarily on retrospective studies that compared hospital patients having cancer of the breast to patients with other diseases for such variables as age, race and socioeconomic status. Lilienfeld and associates[5] used as controls healthy women from the same community as the women with cancer of the breast in studying the epidemiology of the disease. Closer comparisons can be achieved by using siblings, one with and one without the disease. Members of the same family are more similar genetically and socioculturally than the cases and controls in studies cited above. Henderson and co-workers[6] published a study on marital and reproductive histories of patients and their sisters but did not consider the possible effect of birth order on their findings.

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This article describes the findings of a small study of 45 pairs of sisters, each pair including one sister with and one without a cancer of the breast. In approximately half of the pairs the patients were older than their sisters. This allowed us to take the order of birth of the patients and their sisters into account as we compared their ages at the time of marriage, through the history and frequency of term pregnancy, and during the interval between marriage and first term pregnancy.

Patients and Methods

Questionnaires were distributed at a meeting of the Marin Mastectomy Service,* Marin County, California, to women in whom cancer of the breast had previously been diagnosed. Information was requested on the marital and reproductive history of the patient and that of a sister without the disease who was nearest to the patient in age. Eighteen pairs of completed questionnaires were received from this group.

Similar information was requested from a group

*This organization's cooperation was important to the study.

of patients with cancer of the breast seen at the University of California, San Francisco, either during a follow-up examination or at the time of the initial diagnosis. Completed questionnaires were received from 27 of these patients and their siblings, bringing the total number studied to 45 pairs of sisters.

Results

Characteristics of the Study Group

Cancer of the breast in patients in this study was diagnosed between 1960 and 1976, except for one case that was diagnosed in 1949. The group was composed of 37 pairs of whites, five pairs of blacks, two pairs of Asians, and one pair of sisters whose race was not recorded. At the time of the study, the patients had a mean age of 51.6 years and a median age of 53.0 years. The sibling was older than the patient in 22 pairs (mean difference in age of 4.2 years and a median difference of 3.5 years), younger in 22 pairs (mean difference of 4.2 years and a median difference of 3.0 years). The remaining pair of sisters was twins.

Age at Marriage

Tables 1 and 2 show the ages of the patients and their sisters at the time of marriage. Six of the patients and three siblings in this study did not marry. As shown in Table 1, the mean age at the time of marriage for the 39 patients was 26.3 years and 22.6 years for their sisters ($p<.01$). The patients married at a later age than their sisters, whether they were older or younger than the sisters; this excludes order of birth as a factor in their later marriages. Table 2 shows findings for the 38 pairs in which both had been married. The mean age at the time of marriage for patients was 4.1 years greater than the mean age for the sisters ($p<.001$). The findings were similar both when patients were older and when the sisters were older. Similar patterns were noted when the median ages at the time of marriage were reviewed.

In five of the 38 pairs in which both were married, the recorded ages at the time of marriage were the same. Of the 33 pairs in which the members were married at different ages, the patient was married at a later age in 26 of the pairs ($p<.001$). The patient was married at a later age in 16 of 19 instances where the sister was younger, and in ten of 14 instances where the sister was older.

Reproductive History of Patients and Their Sisters

When we calculated our results, we used Lilienfeld's definition of "term pregnancy"[5]—a pregnancy of at least four months' duration. Of the 38 pairs in which both members were married, 34 sisters (Table 3) experienced at least one term pregnancy compared with 26 of the patients ($p<.05$). This pattern primarily applied to pairs in which the patient was older than the sister. There were 12 pairs in which one member of the pair had at least one pregnancy and the other did not. In ten of these 12 pairs, it was the patient who had no pregnancies ($p<.02$).

For the 24 pairs in which both members were married and both had term pregnancies (Table 4), the mean interval between the time of marriage and the first pregnancy was longer for patients (three years) than for their sisters (one year) ($p<.10$). This pattern was again noted both when the patient was older than the sister and when the sister was older than the patient. A similar finding was noted when the median interval between marriage and the first pregnancy was studied.

Table 5 shows that the sisters tended to have

TABLE 1.—*Age at Marriage by Birth Order (all members who had married)*

	*All Pairs**		*Patient Older*		*Patient Younger*	
	Patients	*Sisters*	*Patients*	*Sisters*	*Patients*	*Sisters*
Mean age (years) ...	26.3	22.6	26.5	21.6	26.0	23.7
No. of individuals.	39	42	20	20	19	21

*Includes one set of twins.

TABLE 2.—*Age at Marriage by Birth Order (both members married)*

	All Pairs		*Patient Older*		*Patient Younger*	
	Patients	*Sisters*	*Patients*	*Sisters*	*Patients*	*Sisters*
Mean age (years) ...	26.5	22.4	27.1	21.1	26.0	23.7
No. of pairs .	38		19		19	

TABLE 3.—*History of Term Pregnancy by Birth Order (both members married)*

	All Pairs		*Patient Older*		*Patient Younger*	
History	*Patients*	*Sisters*	*Patients*	*Sisters*	*Patients*	*Sisters*
Term pregnancy .	26	34	12	19	14	15
No term pregnancy .	12	4	7	0	5	4
TOTAL	38	38	19	19	19	19

more term pregnancies than the patients with a mean of 2.6 for the sisters, and 1.7 for the patients ($p<.01$). This pattern is also found when birth order is taken into account and also when the median values are examined.

Table 6 summarizes the relative number of term pregnancies of patients compared with their sisters. The patient had fewer term pregnancies than the sister in 24 of 33 pairs ($p<.01$) in which differences in the number of term pregnancies were noted. Again, birth order was not a factor.

Age at Menarche and Contraceptive Practices

The distribution of recorded ages at menarche was essentially the same for both the patients and their siblings. There was no suggestion of differences in contraceptive practices between patients and controls from responses to the questionnaires in this limited study.

Discussion

A number of studies, primarily using hospital patients with other diseases as controls, have reported a higher percentage of breast cancer patients who were never married. Those with cancer of the breast who did marry, married at an older age, waited longer to have the first child and had fewer term pregnancies than those who did not have the disease. By using sisters as controls, this study was able to narrow the sociocultural and biological differences in the study population. In approximately half of the pairs, the patients were older than their sisters. Because of this distribution, birth order could be considered in comparing marital and reproductive histories of the patients and their sisters. As in previous investigations, fewer of the patients married than the sisters, and those who did were married at a later age, bore fewer children, and experienced a longer delay between marriage and first term pregnancy. These findings were independent of birth order.

The findings of this study are consistent with the current view that early marriage and reproductive history cause hormone changes which reduce the risks of future cancer of the breast. Also, they are consistent with the hypothesis that behavioral factors during adolescence or young adulthood may, in unknown ways, make early marriage and reproduction less desirable to women in whom breast cancer will develop later. Mechanisms for the latter hypothesis can only be speculated upon, but might be hormonal/genetic processes interacting with the cultural factors that influence marriage and reproductive practices.

As attitudes and practices relating to marriage and reproduction change, it may be increasingly difficult in the future to characterize the experiences of patients with cancer of the breast and their siblings. In order to carry out epidemiologic studies parallel to this one, it may be necessary to seek out unique groups whose lifestyles have remained relatively stable.

TABLE 4.—*Interval Between Marriage and First Term Pregnancy by Birth Order (both members married and had term pregnancies)*

	All Pairs		Patient Older		Patient Younger	
	Patients	Sisters	Patients	Sisters	Patients	Sisters
Mean (years)	3.0	1.8	2.2	1.8	3.8	1.8
No. of pairs ..	24		12		12	

TABLE 5.—*Term Pregnancies by Birth Order (both members married)*

	All Pairs		Patient Older		Patient Younger	
	Patients	Sisters	Patients	Sisters	Patients	Sisters
Mean	1.7	2.6	1.5	2.9	1.8	2.3
No. of pairs .	38		19		19	

TABLE 6.—*Pairs by Relative Number of Term Pregnancies and Birth Order (both members married)*

Relative Number of Term Pregnancies	All Pairs	Patient Older	Patient Younger
Patient had fewer .	24	14	10
Sister had fewer .	9	3	6
No difference	5	2	3
TOTAL	38	19	19

REFERENCES

1. Lilienfeld AM: The epidemiology of breast cancer. Cancer Res 23:1503-1513, Oct 1963
2. Shapiro S, Strax P, Venet L, et al: The search for risk factors in breast cancer. Am J Pub Hlth 58:820-835, May 1968
3. Zippin C: The epidemiology of breast cancer. Oncology 23: 93-98, 1969
4. MacMahon B, Cole P, Brown J: Etiology of human breast cancer: A review. J Natl Cancer Inst 50:21-24, Jan 1973
5. Lilienfeld AM, Coombs J, Bross IDJ, et al: Marital and reproductive experience in a community-wide epidemiological study of breast cancer. Johns Hopkins Med J 136:156-162, Apr 1975
6. Henderson BE, Gerkins V, Rosario I, et al: Elevated serum levels of estrogen and prolactin in daughters of patients with breast cancer. N Engl J Med 293:790-795, Oct 1975